EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	31752	seeding	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 08:03
S2	5884	supersaturated solution	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/29 22:04
S3	593	S1 and S2	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/29 22:04
S4	16052	crystallisation step	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/29 22:05
S5	199	S3 and S4	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/29 22:05
S6	28	"6428583"	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 08:03
S7	43	"5314506"	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 11:22
S8	43	dexloxiglumide	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 12:13
S9	2197892	compositions	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 11:23
S10	41	S8 and S9	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 11:28
S11	3	"5602179"	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 12:40
S12	214	562/448	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 12:51

EAST Search History

S13	311	562/455	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 12:45
S14	193	562/400	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 12:45
S15	8105	francesco.in.	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 13:20
S16	141	makovec.in.	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 13:21
S17	242	rovati.in.	US-PGPUB; USPAT; EPO; DERWENT	WITH	ON	2007/07/30 13:22

result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:22:53 ON 30 JUL 2007

=> file caplus
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'CAPLUS' ENTERED AT 12:23:06 ON 30 JUL 2007
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FILE COVERS 1907 - 30 Jul 2007 VOL 147 ISS 6
FILE LAST UPDATED: 29 Jul 2007 (20070729/ED)

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=> s xp002306786
L1 0 XP002306786

=> d XP002306786
L1 HAS NO ANSWERS
L1 0 SEA FILE=CAPLUS ABB=ON PLU=ON XP002306786

=> d XP002306781
L1 HAS NO ANSWERS
L1 0 SEA FILE=CAPLUS ABB=ON PLU=ON XP002306786

=> s 2002:580170
43116 2002
0 580170
L2 0 2002:580170
(2002(W)580170)

=> s 2002:580170/CA
'CA' IS NOT A VALID FIELD CODE
L3 0 2002:580170/CA

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	8.85	9.06

STN INTERNATIONAL LOGOFF AT 12:26:54 ON 30 JUL 2007

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssptalxn1621

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

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NEWS	2	MAR 15	WPIDS/WPIX enhanced with new FRAGHITSTR display format
NEWS	3	MAR 16	CASREACT coverage extended
NEWS	4	MAR 20	MARPAT now updated daily
NEWS	5	MAR 22	LWPI reloaded
NEWS	6	MAR 30	RDISCLOSURE reloaded with enhancements
NEWS	7	APR 02	JICST-EPLUS removed from database clusters and STN
NEWS	8	APR 30	GENBANK reloaded and enhanced with Genome Project ID field
NEWS	9	APR 30	CHEMCATS enhanced with 1.2 million new records
NEWS	10	APR 30	CA/CAplus enhanced with 1870-1889 U.S. patent records
NEWS	11	APR 30	INPADOC replaced by INPADOCDB on STN
NEWS	12	MAY 01	New CAS web site launched
NEWS	13	MAY 08	CA/CAplus Indian patent publication number format defined
NEWS	14	MAY 14	RDISCLOSURE on STN Easy enhanced with new search and display fields
NEWS	15	MAY 21	BIOSIS reloaded and enhanced with archival data
NEWS	16	MAY 21	TOXCENTER enhanced with BIOSIS reload
NEWS	17	MAY 21	CA/CAplus enhanced with additional kind codes for German patents
NEWS	18	MAY 22	CA/CAplus enhanced with IPC reclassification in Japanese patents
NEWS	19	JUN 27	CA/CAplus enhanced with pre-1967 CAS Registry Numbers
NEWS	20	JUN 29	STN Viewer now available
NEWS	21	JUN 29	STN Express, Version 8.2, now available
NEWS	22	JUL 02	LEMBASE coverage updated
NEWS	23	JUL 02	LMEDLINE coverage updated
NEWS	24	JUL 02	SCISEARCH enhanced with complete author names
NEWS	25	JUL 02	CHEMCATS accession numbers revised
NEWS	26	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS	27	JUL 16	CAplus enhanced with French and German abstracts
NEWS	28	JUL 18	CA/CAplus patent coverage enhanced
NEWS	29	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS	30	JUL 30	USGENE now available on STN

NEWS EXPRESS 29 JUNE 2007: CURRENT WINDOWS VERSION IS V8.2,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

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 NEWS IPC8      For general information regarding STN implementation of IPC 8

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FILE 'HOME' ENTERED AT 12:27:35 ON 30 JUL 2007

=> file caplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'CAPLUS' ENTERED AT 12:27:51 ON 30 JUL 2007
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FILE LAST UPDATED: 29 Jul 2007  (20070729/ED)

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=> s CA: 2002:580170
        769528 CA
         12937 CAS
        780451 CA
                  (CA OR CAS)
         43116 2002
             0 580170
L1           0 CA: 2002:580170
                  (CA(W)2002(W)580170)

=> s CA580170
L2           0 CA580170

=> s580170
S580170 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).
```

```
=> s 580170/ca
'CA' IS NOT A VALID FIELD CODE
L3            0 580170/CA

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         8.98       9.19

FILE 'REGISTRY' ENTERED AT 12:29:13 ON 30 JUL 2007
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STRUCTURE FILE UPDATES:   29 JUL 2007  HIGHEST RN 943590-78-1
DICTIONARY FILE UPDATES:  29 JUL 2007  HIGHEST RN 943590-78-1

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predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> s 2002:580170/ca
NUMERIC VALUE NOT VALID '2002:580170'
L4            0 2002:580170/CA

=> s XP002306781
L5            0 XP002306781

=> FIL 1MOBILITY
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        11.25      20.44

FILE '1MOBILITY' ENTERED AT 12:31:17 ON 30 JUL 2007
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 FILE COVERS 1936 TO 5 Jul 2007 (20070705/ED)

 1MOBILITY and 2MOBILITY, which together comprise the Global Mobility
 Database, can be accessed and searched together through the file
 cluster MOBILITY.  Type FILE MOBILITY to enter this cluster.

=>

---Logging off of STN---


=>
Executing the logoff script...
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=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     1.51      21.95

STN INTERNATIONAL LOGOFF AT 12:31:38 ON 30 JUL 2007


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Welcome to STN International!  Enter x:x

LOGINID:ssptalxn1621

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page for STN Seminar Schedule - N. America
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 NEWS  4  MAR 20   MARPAT now updated daily
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 NEWS  7  APR 02   JICST-EPLUS removed from database clusters and STN
 NEWS  8  APR 30   GENBANK reloaded and enhanced with Genome Project ID field
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 NEWS 10  APR 30   CA/CAplus enhanced with 1870-1889 U.S. patent records
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 NEWS 12  MAY 01   New CAS web site launched
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 NEWS 14  MAY 14   RDISCLOSURE on STN Easy enhanced with new search and display
                   fields
 NEWS 15  MAY 21   BIOSIS reloaded and enhanced with archival data
 NEWS 16  MAY 21   TOXCENTER enhanced with BIOSIS reload
 NEWS 17  MAY 21   CA/CAplus enhanced with additional kind codes for German
                   patents
 NEWS 18  MAY 22   CA/CAplus enhanced with IPC reclassification in Japanese
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 NEWS 19  JUN 27   CA/CAplus enhanced with pre-1967 CAS Registry Numbers
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 NEWS 22  JUL 02   LEMBASE coverage updated
 NEWS 23  JUL 02   LMEDLINE coverage updated
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 NEWS 27  JUL 16   CAplus enhanced with French and German abstracts
 NEWS 28  JUL 18   CA/CAplus patent coverage enhanced
 NEWS 29  JUL 26   USPATFULL/USPAT2 enhanced with IPC reclassification
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               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

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FILE 'HOME' ENTERED AT 12:34:01 ON 30 JUL 2007

=> file caplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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=> s dexloxiglumide
L1          40 DEXLOXIGLUMIDE

=> d L1 1-40 bib abs

L1   ANSWER 1 OF 40  CAPLUS  COPYRIGHT 2007 ACS on STN
AN   2007:466133  CAPLUS
DN   146:515153
TI   Effect of CCK-1 receptor blockade on ghrelin and PYY secretion in men
AU   Degen, Lukas; Drewe, Juergen; Piccoli, Franziska; Grani, Karin; Oesch,
     Sibylle; Bunea, Raluca; D'Amato, Massimo; Beglinger, Christoph
CS   Division of Gastroenterology and Clinical Research Centre, University
     Hospital Basel, Basel, Switz.
SO   American Journal of Physiology (2007), 292(4, Pt. 2), R1391-R1399
     CODEN: AJPHAP; ISSN: 0002-9513
PB   American Physiological Society
DT   Journal
LA   English
AB   Cholecystokinin (CCK), peptide YY (PYY), and ghrelin have been proposed to
     act as satiety hormones.  CCK and PYY are stimulated during meal intake by
```

the presence of nutrients in the small intestine, especially fat, whereas ghrelin is inhibited by eating. The sequence of events (fat intake followed by fat hydrolysis and CCK release) suggests that this process is crucial for triggering the effects. The aim of this study was therefore to investigate whether CCK mediated the effect of intraduodenal (ID) fat on ghrelin secretion and PYY release via CCK-1 receptors. Thirty-six male volunteers were studied in three consecutive, randomized, double-blind, cross-over studies:. Twelve subjects received an ID fat infusion with or without 120 mg orlistat, an irreversible inhibitor of gastrointestinal lipases, compared with vehicle;. Twelve subjects received ID long-chain fatty acids (LCF), ID medium-chain fatty acids (MCF), or ID vehicle; and. Twelve subjects received ID LCF with and without the CCK-1 receptor antagonist dexloxiglumide (Dexlox) or ID vehicle plus i.v. saline (placebo). ID infusions were given for 180 min. The effects of these treatments on ghrelin concns. and PYY release were quantified. Plasma hormone concns. were measured in regular intervals by specific RIA systems. ID fat induced a significant inhibition in ghrelin levels and a significant increase in PYY concns. Inhibition of fat hydrolysis by orlistat abolished both effects. LCF significantly inhibited ghrelin levels and stimulated PYY release, whereas MCF were ineffective compared with controls. Dexlox administration abolished the effect of LCF on ghrelin and on PYY. ID fat or LCF significantly stimulated plasma CCK compared with saline. MCF did not stimulate plasma CCK release. In summary, fat hydrolysis is essential to induce effects on ghrelin and PYY through the generation of LCF, whereas MCF are ineffective. Furthermore, LCF stimulated plasma CCK release, suggesting that peripheral CCK is the mediator of these actions. The CCK-1 receptor antagonist Dexlox abolished the effect of ID LCF, on both ghrelin and PYY. Generation of LCF through hydrolysis of fat is a critical step for fat-induced inhibition of ghrelin and stimulation of PYY in humans; the signal is mediated via CCK release and CCK-1 receptors.

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 2 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:72340 CAPLUS
DN 146:219932
TI Pharmacokinetic profile of dexloxiglumide
AU Persiani, Stefano; D'Amato, Massimo; Jakate, Abhijeet; Roy, Partha; Wangsa, Julie; Kapil, Ram; Rovati, Lucio C.
CS Departments of Clinical Pharmacology and Drug Metabolism, Pharmacokinetics and Dynamics, Rotta Research Laboratorium-Rottapharm, Monza, Italy
SO Clinical Pharmacokinetics (2006), 45(12), 1177-1188
CODEN: CPKNDH; ISSN: 0312-5963
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review. Dexloxiglumide is a potent and selective cholecystokinin type 1 (CCK1) receptor antagonist currently under development in a variety of diseases affecting the gastrointestinal tract such as gastro-oesophageal reflux disease, irritable bowel syndrome (IBS), functional dyspepsia, constipation and gastric emptying disorders. In female patients with constipation-predominant IBS, clin. efficacy has been demonstrated following administration of dexloxiglumide 200mg three times daily. Dexloxiglumide is rapidly and extensively absorbed after single oral administration in humans with an absolute bioavailability of 48%. The incomplete bioavailability is due to both incomplete absorption and hepatic first-pass effect. Following multiple-dose administration of 200mg three times daily, the accumulation is predictable, indicating time-independent pharmacokinetics. In addition, dexloxiglumide pharmacokinetics are dose-independent after both single and repeated oral three-times-daily doses in the dose range 100-400mg. Dexloxiglumide absorption window extends from the jejunum to the colon and the drug is a substrate and a weak inhibitor of P-glycoprotein and multidrug resistance protein 1. Plasma protein binding

of dexloxiglumide is 94-98% and the drug has a moderate to low volume of distribution in humans. Systemic clearance of dexloxiglumide is moderate and cytochrome P 450 (CYP) 3A4/5 and CYP2C9 have been implicated in the metabolism of dexloxiglumide to produce O-dimethyl dexloxiglumide. This metabolite is further oxidised to dexloxiglumide carboxylic acid. These two major metabolites (accounting for up to 50% of dexloxiglumide elimination) have been identified. However, in human plasma the unchanged drug represents the major (up to 91%) component of the metabolic profile. The parent drug is believed to be the major contributor to the efficacy of the compound, since its major metabolites are pharmacol. inactive. In addition, the drug is a single isomer chiral drug (eutomer) that does not undergo chiral inversion into its pharmacol. inactive enantiomer (distomer). After oral administration of 14C-dexloxiglumide, radioactivity is mainly excreted in bile and in faeces (74% of dose) with much lower excretion in urine (20% of dose). Renal excretion of unchanged dexloxiglumide is low (7% of dose in urine and faeces, 1% of dose in urine) and is dose-independent in the dose range 100-400mg. As the kidney is a minor contributor to the elimination of dexloxiglumide and/or its metabolites in humans, the pharmacokinetics of the drug should not be affected in patients with renal insufficiency. The pharmacokinetics of dexloxiglumide are also not affected by age, sex and administration with a high-fat breakfast. Mild and moderate liver impairment do not affect the pharmacokinetics of dexloxiglumide but severe liver impairment causes increases in systemic exposure to dexloxiglumide and O-dimethyl dexloxiglumide. Thus, the drug should be prescribed with caution in patients with severe hepatic impairment even though no dose adjustment is warranted. The results of different drug interaction studies have indicated that no clin. relevant metabolic and concomitant drug-drug interactions are expected during the clin. use of dexloxiglumide.

RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 3 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:984514 CAPLUS
DN 146:435468
TI Signal Transduction Pathways Mediating CCK-8S-Induced Gastric Antral Smooth Muscle Contraction
AU Si, Xin-Min; Huang, Lei; Paul, Shelley Chireyath; An, Ping; Luo, He-Sheng
CS Department of Digestive Medicine, Renmin Hospital, Wuhan University, Hubei, Peop. Rep. China
SO Digestion (2006), 73(4), 249-258
CODEN: DIGEBW; ISSN: 0012-2823
PB S. Karger AG
DT Journal
LA English
AB Aim: To investigate the functional and mol. mechanisms by which sulfated cholecystokinin octapeptide (CCK-8S) regulates calcium mobilization in gastric antral smooth muscle cells (SMCs) of rats. Methods: Isotonic contraction of antral strips was recorded using a polyphysiograph. Immunopptn. was used to determine the regulatory effect of protein kinase C (PKC) on regulating the phosphorylation of the type III inositol 1,4,5-triphosphate receptor (InsP3R3) in gastric SMCs. Alterations in the intracellular calcium ([Ca2+]i) concentration were assayed using fura-2/AM-loaded microspectrofluorometry, and the L-type calcium current (ICa-L) was recorded by patch-clamp techniques. Results: CCK-8S (5 + 10-8 mol/l) significantly increased the mean contractile amplitude of circular muscle by 61.85 ± 12.67% and the frequency of longitudinal muscle by 57.91 ± 15.70% in gastric antral strips, which were suppressed by dexloxiglumide or thapsigargin (TG) and BAPTA-AM (BA). Treatment with chelerythrine (5 + 10-8 mmol/l) significantly inhibited the CCK-8S-increased phosphorylation of InsP3R3 in SMCs. The amplitudes of the CCK-8S-triggered [Ca2+]i concentration oscillations were reduced in a

dose-dependent manner when the SMCs were pretreated with increasing concns. of PMA (from 10-8 to 10-5 mol/l). On removal of extracellular calcium or blocking ICa-L by nifedipine, a smaller but significant rise in the [Ca2+]i concentration was still elicited by CCK-8S. When [Ca2+]i was depleted by the administration of 10-5 mol/l TG and 10-5 mol/l BA or blocked by the calcium-dependent chloride current (ICl-Ca) by giving 5 + 10-6 mol/l niflumic acid, the CCK-8S-intensified ICa-L (from -56.42 ± 6.57 to -88.54 ± 5.71 pA) was apparently inhibited by 90.34 ± 4.71% and 82.59 ± 4.24%. Conclusions: These results demonstrate that the CCK-8S-evoked [Ca2+]i concentration increase in gastric antral SMCs depends on the release of [Ca2+]i stores which are neg. regulated by PKC-mediated phosphorylation of InsP3R3. Released calcium in turn activates ICa-L through the activation of ICl-Ca, ultimately resulting in the contraction of the gastric smooth muscle.

RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 4 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:899364 CAPLUS
DN 145:327448
TI Twenty years of non-peptide CCK1 receptor antagonists: all that glitters is not gold
AU Varnavas, Antonio; Lassiani, Lucia
CS Department of Pharmaceutical Sciences, University of Trieste, Trieste, 34127, Italy
SO Expert Opinion on Therapeutic Patents (2006), 16(9), 1193-1213
CODEN: EOTPEG; ISSN: 1354-3776
PB Informa Healthcare
DT Journal; General Review
LA English
AB A review. During the last 20 years, pharmaceutical industry and academic efforts have led to several structurally unrelated classes of non-peptide cholecystokinin-1 receptor (CCK1-R) antagonists. Due to the lack of high resolution structure of CCK1-R and its peptide ligand, different strategies to design antagonists have been adopted. The rational design, based on conformational studies of the endogenous ligand, has provided the so-called peptoid' derivs. and conformationally restricted peptoids, whereas all of the other non-peptide antagonists derived by empirical and/or conventional approaches, including the chemical manipulation of natural products, disconnection strategies and the use of single key amino acids. All of these strategies include a final optimization step of the obtained lead compound performed by chemical modifications. The CCK1-R antagonists, in addition to providing a better characterization of the CCK1-R receptor subtype as pharmacol. tools and improving the knowledge of the physiol. and pathol. role(s) of CCK, may possess therapeutic potential in humans. As the complex biol. effects of CCK mediated by CCK1-R in the CNS are not yet completely established, the therapeutic potential of these antagonists at present is limited to the gastrointestinal system disorders. Up until now, loxiglumide and its R-enantiomer (dexloxiglumide) along with lintitript are the CCK1-R antagonists at the most advanced stage of clin. research in gastroenterol.

RE.CNT 139 THERE ARE 139 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 5 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:788338 CAPLUS
DN 145:224869
TI Altering intestinal motility and absorption of hydrophobic compounds through the use of agonists and/or antagonists of the cholecystokinin-1 receptor
IN Kopin, Alan S.; Carey, Martin; Wang, David
PA New England Medical Center, USA
SO U.S. Pat. Appl. Publ., 19pp.
CODEN: USXXCO
DT Patent

LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2006177438	A1	20060810	US 2005-53553	20050208
PRAI	US 2005-53553		20050208		

AB This invention presents methods of increasing intestinal motility rates in order to decrease intestinal absorption of cholesterol. Furthermore, this invention presents methods of modulating intestinal motility in order to influence pos. the amount of drug or nutrient absorption from the intestine, especially of hydrophobic drugs or nutrients. The instant methods comprise modulating the rate of intestinal motility through the use of agonists and/or antagonists of the cholecystokinin-1 receptor. The inventors have discovered that hypercholesterolemia can be treated using methods that increase intestinal motility, preferably small intestinal motility, by increasing the activity of the CCK 1 receptor through the use of CCK-1R agonists. A decreased transit time of cholesterol-containing material in the intestine, particularly in the small intestine, mediated by increased intestinal motility caused by activation of the CCK 1 receptor, results in a decreased amount of cholesterol being absorbed by the intestines, in particular by the small intestine. The present inventors have also discovered that the amount of intestinal absorption of drug or nutrient materials, including hydrophobic drugs or nutrients, can be increased using methods that decrease intestinal motility, preferably small intestinal motility, by decreasing the activity of the CCK 1 receptor through the use of CCK-1R antagonists.

L1 ANSWER 6 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:650778 CAPLUS
DN 145:181104
TI A novel, quantitative bio-assay for cholecystokinin type-1 receptor activity in the anesthetized rat
AU Freedman, Jamie M.; Barrett, Terrance D.; Shankley, Nigel P.
CS Physiological Systems, Johnson & Johnson Pharmaceutical Research & Development, L.L.C., San Diego, CA, 92121, USA
SO Journal of Pharmacological and Toxicological Methods (2006), 54(1), 36-41
CODEN: JPTMEZ; ISSN: 1056-8719
PB Elsevier B.V.
DT Journal
LA English
AB Cholecystokinin type-1 (CCK1) receptors mediate many of the physiol. functions of CCK including delay of gastric emptying, pancreatic enzyme secretion, intestinal motility and gallbladder contractility. Existing in-vivo assays for the quant. measurement of CCK1 receptor mediated function are generally variable, limited in precision and require a relatively large number of animals to obtain statistically meaningful data. We found that they did not provide robust pharmacokinetic-pharmacodynamic data for profiling compds. acting at these receptors. Accordingly, here we describe a novel rat duodenal contractility assay that addresses these problems. Rats were anesthetized and a saline-filled balloon was inserted through the body of the stomach and secured in the duodenum .apprx. 1 cm from the pyloric sphincter for measurement of intra-lumenal pressure. Studies were performed to determine a dose, rate and frequency of administration of CCK8S that produced a readily quantifiable response. Results showed that initial expts. revealed that sustained exposure to CCK8S resulted in the rapid development of tachyphylaxis. After investigating different dosing paradigms, it was found that pulsatile delivery of CCK8S (i.v. infusion for 1 min every 10 min) produced a readily quantifiable contractile response that did not exhibit tachyphylaxis. The assay response output was defined as the number of contractions > 5 mm Hg over baseline. The contractions were blocked in a dose-dependent manner by i.v. bolus injections of the CCK1 receptor antagonists, Dexloxiglumide (2 and 20 μmol/kg), and Devazepide (3-100 nmol/kg) but not by the CCK2 receptor antagonist Gastrazole (10 μmol/kg). Thus, a novel, simple, high quality assay for

the quantification of the in-vivo activity of CCK1 receptor ligands is described. CCK8S delivered by pulsatile i.v. infusion to anesthetized rats produced a burst of contractile activity of the duodenum mediated by CCK1 receptors. This activity was highly reproducible and sustained for more than 3 h providing an assay that circumvents problems associated with agonist-induced tachyphylaxis.

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 7 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:606197 CAPLUS
DN 145:56424
TI A composition comprising PP (pancreatic polypeptide) for the treatment of gastrointestinal disorders
IN Nilsson, Henrik
PA Aditech Pharma AB, Swed.
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2006063596	A2	20060622	WO 2005-DK796	20051215
	WO 2006063596	A3	20060824		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI DK 2004-1939 A 20041215
AB The present invention relates to PP or functional equivalent thereof for use in pharmaceutical compns. The pharmaceutical compns. are in particular useful in the treatment of functional gastrointestinal disorders, such as irritable bowel disease and functional dyspepsia. The invention further relates to methods of treatment using said compns. Further included is the combination of PP or functional equivalent thereof with a secondary active ingredient such as an anti-emetic drug.

L1 ANSWER 8 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:469836 CAPLUS
DN 144:460844
TI Dopamine 3 receptor agonist and antagonist treatment of gastrointestinal motility disorders
IN Pasricha, Pankaj Jay; Micci, Maria-Adelaide
PA The Board of Regents of the University of Texas System, USA
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2006052626	A2	20060518	WO 2005-US39736	20051103
	WO 2006052626	A3	20060727		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,

KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX,
MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM

US 2006116350 A1 20060601 US 2005-266686 20051103
PRAI US 2004-624603P P 20041103

AB The invention discloses that systemic activation of dopamine 3 receptor (D3R) significantly delays gastric emptying in rat, suggesting that D3R plays an important role in the regulation of gastric motility. Specific D3R antagonist, nafadotride, was shown to partially reverse the effect of dopamine on gastric emptying. The invention also discloses that D3R agonists and antagonists can be used to treat gastrointestinal motility disorders.

L1 ANSWER 9 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:386422 CAPLUS
DN 144:405908
TI cDNA and polypeptide sequences for canine cholecystokinin 1 receptor and their use for drug screening
IN Dai, Heng; Morton, Magda F.; Pyati, Jayashree; Shankley, Nigel P.
PA Janssen Pharmaceutica N.V., Belg.
SO PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2006044352	A2	20060427	WO 2005-US36476	20051011

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ,
NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG,
SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,
YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM

PRAI US 2004-617888P P 20041012

AB Canine cholecystokinin 1 (CCK1/CCKA) receptor materials are described, such as polypeptides having amino acid sequences corresponding to SEQ ID Nos.: 14, 15, and 16 or functional variants thereof and polynucleotides expressing them having nucleic acid sequences corresponding to SEQ ID Nos.: 11, 12, and 13 or complements thereof. Such materials are useful as reagents in drug screening assays to identify compds. having CCK1R-modulating activity. Canine CCK1 receptor cDNA was cloned from gallbladder tissue based on sequence homol. with conserved regions of human and rat CCK1 receptor cDNAs. In addition to a wild-type canine cDNA, two variants with 3 or 6 amino acid differences were cloned from the canine gallbladder tissue. The canine CCK1 receptors were characterized by radioligand binding studies. No significant differences were observed in the affinity of L-364,718, L-365,260, YF476, YM022, and dexloxiglumide between the canine and human CCK1 receptor. There were no significant differences in the affinity values of the CCK receptor selective ligands between the wild-type and variant #1 canine CCK1 receptors. The variant #2 canine CCK1 receptor did not bind the ligand [125I]-BH-CCK-8S or the protein was expressed at too low a level to detect

binding in the assay.

L1 ANSWER 10 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:100738 CAPLUS
DN 144:198849
TI Novel dosage form comprising modified-release and immediate-release active ingredients
IN Vaya, Navin; Karan, Rajesh Singh; Sadanand, Sunil; Gupta, Vinod Kumar
PA India
SO U.S. Pat. Appl. Publ., 49 pp., Cont.-in-part of U.S. Ser. No. 630,446.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2006024365	A1	20060202	US 2005-134633	20050519
	IN 2002MU00697	A	20040529	IN 2002-MU697	20020805
	IN 193042	A1	20040626		
	IN 2002MU00699	A	20040529	IN 2002-MU699	20020805
	IN 2003MU00080	A	20050204	IN 2003-MU80	20030122
	IN 2003MU00082	A	20050204	IN 2003-MU82	20030122
	US 2004096499	A1	20040520	US 2003-630446	20030729
PRAI	IN 2002-MU697	A	20020805		
	IN 2002-MU699	A	20020805		
	IN 2003-MU80	A	20030122		
	IN 2003-MU82	A	20030122		
	US 2003-630446	A2	20030729		

AB A dosage form comprising of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg; a process for preparing the dosage form. Tablets containing 10 mg sodium pravastatin and 1000 mg niacin were prepared The release of sodium pravastatin after 24 h was 67.7%, and the release of niacin after 1 h was 84.1%.

L1 ANSWER 11 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1270583 CAPLUS
DN 144:266530
TI Effect of azole antifungals ketoconazole and fluconazole on the pharmacokinetics of dexloxiglumide
AU Jakate, Abhijeet S.; Roy, Partha; Patel, Alpita; Abramowitz, Wattanaporn; Persiani, Stefano; Wangsa, Julie; Kapil, Ram
CS Department of Clinical Pharmacology and Drug Dynamics, Forest Research Institute, Jersey City, NJ, USA
SO British Journal of Clinical Pharmacology (2005), 60(5), 498-507
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell Publishing Ltd.
DT Journal
LA English
AB Aims: Dexloxiglumide is a new CCK1 receptor antagonist under investigation for treatment of functional gastrointestinal disorders and is metabolized by CYP3A4 and CYP2C9. The objectives of these two sep. randomized, two-period, two-treatment crossover studies were to investigate the effects of steady-state ketoconazole, a model CYP3A4 inhibitor (Study 1), and steady-state fluconazole, a model CYP2C9 inhibitor (Study 2), on the pharmacokinetics of dexloxiglumide in healthy subjects. Methods: Plasma samples were analyzed for dexloxiglumide and its primary metabolites: O-demethyl dexloxiglumide (ODM; Study 1 and 2) and dexloxiglumide carboxylic acid (DCA; Study 2). Results: Following ketoconazole coadministration, dexloxiglumide Cmax increased by 32% (90% confidence intervals (CI) 112-154), with unchanged ODM Cmax; AUC of dexloxiglumide and ODM increased by 36% (90% CI 124-140 and

128-142, resp.). No changes were observed in dexloxiglumide or ODM t1/2. Fluconazole coadministration caused a 77% increase (90% CI 154-204) in dexloxiglumide Cmax, no change in ODM Cmax and a 32% decrease (90% CI 62-75) in DCA Cmax. Fluconazole coadministration resulted in a 2.5-fold increase (90% CI 235-267) in dexloxiglumide AUC, 40% increase (90% CI 136-156) in ODM AUC and an 18% decrease (90% CI 82-94) in DCA AUC. The t1/2 of all three analytes increased by approx. 2-fold with fluconazole coadministration (P-value <0.05). Conclusions: Ketoconazole caused a minimal increase while fluconazole caused a moderate increase in dexloxiglumide systemic exposure with no change in the adverse event profile of dexloxiglumide.

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 12 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1063146 CAPLUS
DN 144:100317
TI The single-dose pharmacokinetics of the novel CCK1 receptor antagonist, dexloxiglumide, are not influenced by age and gender
AU Roy, P.; Wangsa, J.; Patel, A.; Nolting, A.; Persiani, St.; Abramowitz, W.; Kapil, R.
CS Department of Clinical Pharmacology and Drug Dynamics, Forest Research Institute, Harborside Financial Center, NJ, USA
SO International Journal of Clinical Pharmacology and Therapeutics (2005), 43(9), 444-451
CODEN: ICTHEK; ISSN: 0946-1965
PB Dustri-Verlag Dr. Karl Feistle
DT Journal
LA English
AB Objective: The effects of age and gender on the single-dose pharmacokinetics of dexloxiglumide, a selective cholecystokinin (CCK1-subtype) receptor antagonist, were assessed in healthy young and elderly male and female subjects. Methods: In total, 24 males and 24 females (12 young and 12 elderly subjects per gender group) received a single oral dose of 200 mg dexloxiglumide under fasted conditions. Mean (range) ages were 23.8 (18 - 32) and 71.3 (66 - 88) years for young and elderly subjects, resp. Anal. of covariance (ANCOVA) with age group and gender as factors and body weight as a covariate was performed on the dexloxiglumide pharmacokinetic parameters of peak plasma concentration (Cmax) and the area under the plasma concentration-time curve (AUC). The p values obtained from ANCOVA were considered for the assessment of age and gender effects. Results: A small (.apprx. 18%) but statistically significant ($p \leq 0.036$) increase in the area under the plasma concentration-time curve from 0 to time of last quantifiable concentration (AUC0-t) and the area under the plasma concentration-time curve from 0 to infinity (AUC0-∞) in elderly compared to young subjects was noted. Given the lack of age effects on the other pharmacokinetic parameters of dexloxiglumide, this limited difference is unlikely to be clin. relevant. Without the adjustment for body wts., female subjects exhibited mean Cmax and AUC values approx. 26% and 36% higher than male subjects; however, these exposure differences did not reach statistical significance ($p > 0.05$) following ANCOVA anal. with body weight as a covariate. Likewise, there were no statistically significant differences ($p > 0.05$) observed for any other pharmacokinetic parameters between young and elderly and between male and female groups. Conclusions: Dose adjustments based on age and gender are not necessary. Dexloxiglumide administration was safe and well tolerated in these subjects.

RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 13 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:823572 CAPLUS
DN 143:199942

TI Pharmaceutical combinations comprising (S)-pantoprazole
IN Huber, Reinhard; Kohl, Bernhard; Kromer, Wolfgang; Simon, Wolfgang-Alexander
PA Altana Pharma A.-G., Germany
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005074931	A1	20050818	WO 2005-EP50336	20050127

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI EP 2004-1757 A 20040128

AB The invention relates to the combination of (S)-pantoprazole and/or its salts and compds., which modify gastrointestinal motility. The invention relates to the combination of (1) a first ingredient (S)-pantoprazole and/or its salts and (2) a second active ingredient, which modifies gastrointestinal motility, selected from a group consisting of 5-HT agonists/antagonists, muscarinic antagonists, κ-opioid receptor agonists, δ-opioid receptor agonists, opioid receptor agonists, dopamine receptor antagonists, cholecystokinin A antagonists, α2 adrenoceptor agonists, N-methyl-D-aspartate receptor antagonists, non-N-methyl-D-aspartate glutamate receptor antagonists, nitric oxide synthase inhibitors, motilin agonists, somatostatin agonists/antagonists, neurotensin agonists/antagonists, vasoactive intestinal peptide antagonists, substance P antagonists, neurokinin antagonists, calcium channel blockers, potassium channel openers, selective serotonin reuptake inhibitors, corticotropin releasing factor antagonists, GABA-A receptor agonists, GABA-B receptor agonists, gastroprokinetics, antiemetics and antispasmodics.

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 14 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:511232 CAPLUS
DN 143:72058
TI Pharmacological analysis of CCK2 receptors up-regulated using engineered transcription factors
AU Morton, Magda F.; Liu, Pei-Qi; Reik, Andreas; de la Rosa, Ragan; Mendel, Matthew; Li, Xiao-Yong; Case, Casey; Pabo, Carl; Moreno, Veronica; Pyati, Jayashree; Shankley, Nigel P.
CS Johnson & Johnson Pharmaceutical Research & Development, L.L.C., San Diego, CA, 92121, USA
SO Regulatory Peptides (2005), 129(1-3), 227-232
CODEN: REPPDY; ISSN: 0167-0115
PB Elsevier B.V.
DT Journal
LA English

AB Designed zinc finger proteins (ZFPs) regulate expression of target genes when coupled to activator or repressor domains. Transfection of ZFPs into cell lines can create expression systems where the targeted endogenous gene is transcribed and the protein of interest can be investigated in its own cellular context. Here we describe the pharmacol. investigation of an expression system generated using CCK2 receptor-selective ZFPs transfected

into human embryonic kidney cells (HEKZFP system). The receptors expressed in this system, in response to ZFP expression, were functional in calcium mobilization studies and the potency of the agonists investigated was consistent with their action at CCK2 receptors (CCK-8S pA50 = 9.05±0.11, pentagastrin pA50 = 9.11±0.13). In addition, binding studies were conducted using [125I]-BH-CCK-8S as radioligand. The saturation binding anal. of this radioligand was consistent with a single population of high affinity CCK receptors (pKD = 10.24). Competition studies were also conducted using a number of previously well-characterized CCK-receptor selective ligands; JB93182, YF476, PD-134,308, SR27897, Dexloxiglumide, L-365,260 and L-364,718. Overall, the estimated affinity values for these ligands were consistent with their interaction at CCK2 receptors. Therefore, CCK2 receptors up-regulated using zinc finger protein technol. can provide an alternative to standard transfection techniques for the pharmacol. anal. of compds.

RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 15 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:465482 CAPLUS
DN 143:71901
TI Molecular cloning, expression and pharmacological characterization of the canine cholecystokinin 1 receptor
AU Morton, Magda Francesca; Pyati, Jayashree; Dai, Heng; Li, Lina; Moreno, Veronica; Shankley, Nigel Paul
CS Johnson & Johnson Pharmaceutical Research & Development, L.L.C, San Diego, CA, 92121, USA
SO British Journal of Pharmacology (2005), 145(3), 374-384
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB The full-length, canine cholecystokinin 1 (CCK1) receptor was cloned from gallbladder tissue using RT-PCR with a combination of primers designed to interact with conserved regions of the human and rat CCK1 receptor, which also shared homol. with the canine genomic sequence. Anal. of the sequence of the canine CCK1 receptor revealed a 1287 base pair product, which encoded a 429 amino-acid protein. This protein was 89% identical to the human and 85% identical to the rat CCK1 receptor. The canine CCK1 receptor was expressed in CHO-K cells for pharmacol. characterization. In competition studies, using [125I]BH-CCK-8S as radioligand, the affinity values estimated for CCK receptor-selective compds. were not significantly different between the canine and human CCK1 receptors (pKI at canine CCK1 receptor; L-364,718 = 8.82, L-365,260 = 6.61, YF476 = 7.91, YM022 = 8.28 and dexloxiglumide = 7.53). Furthermore, the selectivity of these compds. between canine CCK1 and CCK2 receptors was consistent with the selectivity between the human CCK1 and CCK2 receptors. Two addnl. forms of the canine CCK1 receptor were identified during the cloning procedure. These had three (variant #1) and six (variant #2) amino-acid differences from the wild-type canine CCK1 receptor. Variant #1 bound [125I]BH-CCK-8S and displayed an identical pharmacol. profile to the wild-type receptor using the ligands described above. No significant binding was measured with variant #2. In conclusion, the authors have cloned and pharmacol. characterized the canine CCK1 receptor. The data obtained will facilitate the interpretation of numerous pharmacol. expts. that have been performed using canine tissue to elucidate the actions of CCK and gastrin.

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 16 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:460641 CAPLUS
DN 144:44965
TI Effect of multiple-dose dexloxiglumide on the pharmacokinetics of oral contraceptives in healthy women

AU Roy, Partha; Jakate, Abhijeet S.; Patel, Alpita; Abramowitz, Wattanaporn; Wangsa, Julie; Persiani, Stefano; Kapil, Ram
CS Department of Clinical Pharmacology and Drug Dynamics, Forest Research Institute, Jersey City, NJ, USA
SO Journal of Clinical Pharmacology (2005), 45(3), 329-336
CODEN: JCPCBR; ISSN: 0091-2700
PB Sage Publications
DT Journal
LA English
AB This study was undertaken to evaluate the effect of dexloxiglumide , a selective cholecystokinin receptor antagonist, on the pharmacokinetics of a combination oral contraceptive (OC). A single-blind, placebo-controlled, 2-period crossover study was conducted in 24 healthy young female subjects who received Ortho Tri-Cyclen containing ethinyl estradiol (EE, 0.035 mg) and norgestimate (NE, 0.180 mg/0.215 mg/0.250 mg per 7-day phase, resp.) for 5 days (days 17-21) concurrently with either 200 mg dexloxiglumide (3 times a day on days 17-20, followed by a single dose on day 21) or matching placebo during 2 consecutive 28-day OC dosing cycles. Plasma was sampled up to 24 h for the determination of EE, NE, and 17-deactyl norgestimate (17-DNE, a rapidly formed pharmacol. active metabolite of NE). The geometric mean ratios (GMRs, dexloxiglumide/placebo) of the plasma concentration-time curve over 24 h with corresponding 90% confidence intervals (CIs) for EE and 17-DNE were 1.21 (1.17-1.26) and 0.92 (0.89-0.95), resp. The GMRs (90% CI) of Cmax for EE and 17-DNE were 1.15 (1.09-1.20) and 0.93 (0.90-0.96), resp. Coadministration of OC and dexloxiglumide was well tolerated and safe. Comparable systemic exposure of EE and 17-DNE in the presence and absence of dexloxiglumide suggests that dexloxiglumide treatment is unlikely to interfere with the safety and efficacy of oral contraceptives based on the anal. of the resulting pharmacokinetic profile.
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 17 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:349550 CAPLUS
DN 143:109434
TI Effect of CCK-1 antagonist, dexloxiglumide, in female patients with irritable bowel syndrome: a pharmacodynamic and pharmacogenomic study
AU Cremonini, Filippo; Camilleri, Michael; McKinzie, Sanna; Carlson, Paula; Camilleri, Christopher E.; Burton, Duane; Thomforde, George; Urrutia, Raul; Zinsmeister, Alan R.
CS Clinical Enteric Neuroscience Translational and Epidemiological Research Program, Gastroenterology Research Unit, Mayo Clinic College of Medicine, Rochester, MN, USA
SO American Journal of Gastroenterology (2005), 100(3), 652-663
CODEN: AJGAAR; ISSN: 0002-9270
PB Blackwell Publishing, Inc.
DT Journal
LA English
AB Cholecystokinin (CCK) is involved in gastrointestinal motor response to meals. The potential role of CCK receptor antagonists in functional gastrointestinal disorders is unclear. To evaluate the effects of dexloxiglumide, a CCK-1 receptor antagonist, on gastrointestinal transit (GIT) and symptoms in patients with constipation-predominant IBS (C-IBS); and to explore the influence of CCK-1 receptor polymorphisms on gut transit and the pharmacodynamic response to therapy. A total of 36 patients with C-IBS and normal to slow baseline colonic transit (CT) were randomized (double-blind, parallel design) to 7 days of dexloxiglumide 200 mg or placebo t.i.d. Daily bowel habits diaries and weekly relief of IBS symptoms were recorded. At the end of treatment, GIT and CT were measured. Peripheral blood DNA was examined for polymorphisms in genes controlling CCK: four related to CCK-1, one to the CCK gene promoter, and one related to CCK-2. The distributions of allelic

variants and association with gastric emptying in response to dexloxiglumide and placebo were assessed. Dexloxiglumide was associated with accelerated gastric emptying t1/2 ($p = 0.004$), and slower ascending colon emptying t1/2 ($p < 0.01$), with no significant effect on overall CT or satisfactory relief of IBS. There was an association between CCK 779T > C polymorphism and slower rate of gastric emptying ($p = 0.04$). Dexloxiglumide accelerates gastric emptying and delays proximal but not overall CT in patients with C-IBS. Dexloxiglumide does not accelerate transit in C-IBS. The role of CCK-1 gene polymorphisms in delaying gastric emptying and in determining response to therapy deserves further study.

RE.CNT 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 18 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:1154650 CAPLUS
DN 142:79937
TI Crystallization method for the preparation of crystalline dexloxiglumide and its pharmaceutical formulations
IN Makovec, Francesco; Rovati, Lucio Claudio
PA Rotta Research Laboratorium S.P.A., Italy; Rottapharm S.P.A.
SO PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004113271	A2	20041229	WO 2004-IB2208	20040621
	WO 2004113271	A3	20050127		
	WO 2004113271	A8	20050324		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2004249526	A1	20041229	AU 2004-249526	20040621
	CA 2529018	A1	20041229	CA 2004-2529018	20040621
	EP 1646607	A2	20060419	EP 2004-743871	20040621
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
	US 2006154987	A1	20060713	US 2005-562013	20051223
PRAI	IT 2003-TO474	A	20030623		
	WO 2004-IB2208	W	20040621		

AB A method for the purification of dexloxiglumide by crystallization from iso-Pr ether is described which permits the production, in a reproducible manner, of a product with morphol. and particle-size characteristics such as favor its use in the preparation of oral pharmaceutical forms on an industrial scale.

L1 ANSWER 19 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:1059201 CAPLUS
DN 142:32977
TI Pharmaceutical combinations of a proton pump inhibitor and a compound which modifies gastrointestinal motility
IN Zimmermann, Peter Jan; Chiesa, M. Vittoria; Palmer, Andreas; Brehm, Christof; Klein, Thomas; Senn-Bilfinger, Joerg; Simon, Wolfgang-Alexander; Kromer, Wolfgang; Grundler, Gerhard; Hanauer, Guido; Buhr, Wilm; Postius, Stefan

PA Altana Pharma A.-G., Germany
SO PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004105795	A1	20041209	WO 2004-EP50936	20040526
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004243444	A1	20041209	AU 2004-243444	20040526
CA 2526566	A1	20041209	CA 2004-2526566	20040526
EP 1644043	A1	20060412	EP 2004-741658	20040526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2006528231	T	20061214	JP 2006-530222	20040526
MX 2005PA12463	A	20060130	MX 2005-PA12463	20051118
US 2006241134	A1	20061026	US 2005-557414	20051118
NO 2005005968	A	20051215	NO 2005-5968	20051215
PRAI EP 2003-11875	A	20030527		
EP 2004-102304	A	20040525		
WO 2004-EP50936	W	20040526		

AB The invention relates to the combination of certain active compds. from the acid pump antagonist class and compds. which modify gastrointestinal motility. The acid pump antagonist class is selected from a tricyclic imidazopyridine and the gastrointestinal motility modifier is selected from a 5-HT-(partial)-agonist/antagonist.
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 20 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:694639 CAPLUS
DN 142:106268
TI Functional dyspepsia: drugs for new (and old) therapeutic targets
AU Cremonini, Filippo; Delgado-Aros, Silvia; Talley, Nicholas J.
CS Clinical Enteric Neuroscience Translational and Epidemiological Research Program, Mayo Clinic College of Medicine, Rochester, MN, 55905, USA
SO Best Practice & Research, Clinical Gastroenterology (2004), 18(4), 717-733
CODEN: BPRCB6
PB Elsevier B.V.
DT Journal; General Review
LA English
AB A review. The therapeutic management of functional dyspepsia remains a major challenge for the gastroenterologist. Current therapies available are based on putative underlying pathophysiol. mechanisms, including gastric acid sensitivity, slow gastric emptying and Helicobacter pylori infection, but only a small proportion of patients achieve symptomatic benefit from these therapeutic approaches. Relatively novel mechanistic concepts under testing include impaired gastric accommodation, visceral hypersensitivity, and central nervous system dysfunction. Serotonergic modulators (e.g. the 5-HT4 agonist tegaserod, the 5-HT3 antagonist alosetron and the 5-HT1P agonist sumatriptan), CCK-1 antagonists (e.g. dexloxiglumide), opioid agonists (e.g. asimadoline), N-methyl-D-aspartate (NMDA) receptor antagonists (e.g dextromethorphan), neurokinin antagonists (e.g. talnetant), capsaicin-like agents and

antidepressants are among the agents currently under investigation. It seems unlikely, however, that targeting a single mechanism with an individual drug will result in complete symptom remission in most cases.
RE.CNT 116 THERE ARE 116 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 21 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:597303 CAPLUS
DN 141:134445
TI Cholecystokinin pathways modulate sensations induced by gastric distension in humans
AU Lal, Simon; McLaughlin, John; Barlow, Josephine; D'Amato, Massimo; Giacovelli, Giampaolo; Varro, Andrea; Dockray, Graham J.; Thompson, David G.
CS Division of Gastro-Intestinal Sciences, Hope Hospital, University of Manchester, Salford, M6 8HD, UK
SO American Journal of Physiology (2004), 287(1, Pt. 1), G72-G79
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB Ingested fat releases CCK, causes gastric relaxation, delays gastric emptying, and limits meal size; however, the mechanistic link among these actions has not been established. Fatty acid release of CCK is chain-length sensitive; dodecanoic acid (C12) induces greater CCK release than decanoic acid (C10). The effect of C12 or C10 on tolerance to subsequent intragastric infusion of liquid was determined in healthy subjects, with and without the CCK1 receptor antagonist dexloxiglumide. Gastric wall relaxation after either fatty acid was assessed by graded volume distension and by barostat; gastric emptying was measured by gastric aspiration and by a [13C]octanoic acid breath technique. C12 released more CCK (mean plasma CCK after vehicle, 4.7 pM; C10, 4.8 pM; C12, 8 pM) and reduced the volume of water (and of 5 and 25% glucose solns.) delivered at maximum tolerance compared with C10 or vehicle (volume of water tolerated after vehicle, 1535 mL; C10, 1335 mL; C12, 842 mL); this effect was abolished by dexloxiglumide. Intragastric vols. were always similar at the limit of tolerance, and, whereas gastric relaxation occurred to similar degrees after the fatty acids, its duration was longer after C12, which also induced a longer delay in half-gastric emptying [t1/2(min) after vehicle, 53; C10, 67; C12, 88]. In conclusion, ingestion of a CCK-releasing fatty acid reduces the tolerated volume of liquid delivered into the stomach, primarily via a CCK1 receptor-mediated delay in gastric emptying.
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 22 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:464729 CAPLUS
DN 141:218262
TI Interaction of dexloxiglumide, a cholecystokinin type-1 receptor antagonist, with human cytochromes P450
AU Hall, Michael; Persiani, Stefano; Cheung, Yen-Ling; Matthews, Anne; Cybulski, Z. Richard; Holding, Jeremy D.; Kapil, Ram; D'Amato, Massimo; Makovec, Francesco; Rovati, Lucio C.
CS Department of In Vitro Metabolism, Huntingdon Life Sciences Ltd, Huntingdon, UK
SO Biopharmaceutics & Drug Disposition (2004), 25(4), 163-176
CODEN: BDDID8; ISSN: 0142-2782
PB John Wiley & Sons Ltd.
DT Journal
LA English
AB Dexloxiglumide (DEX) is a cholecystokinin type-1 receptor antagonist under development for the treatment of constipation-predominant irritable bowel syndrome. Studies of the potential interaction of DEX with human cytochromes P 450 (CYPs) were conducted in vitro. DEX (300

μM), both with and without a 15-min preincubation, was incubated with pooled human liver microsomes and substrates selective for each of eight CYPs. This resulted in > 30% inhibition of tolbutamide 4-methyl-hydroxylase (CYP2C9/10) and lauric acid 11-hydroxylase (CYP2E1) activities. Mean Ki (SD) for CYP2C9/10 and CYP2E1 were 69.0 (24.3) and 426 (60) μM, resp. Incubations of [14C]DEX with pooled human liver microsomes produced one major phase I metabolic fraction, with Vmax = 131 pmol/min/mg protein and Km = 23.7 μM. Further incubations with (i) liver microsomes from 16 individual donors (correlation anal.), (ii) Supersomes and (iii) selective chemical inhibitors, implicated CYP3A4/5, CYP2B6 and CYP2C9 in the formation of this component. Thus, DEX interacts with CYP2C9 both as inhibitor (Ki = 69.0 μM) and as substrate in vitro. However, based on the maximum concentration (27 μM) after repeated oral doses of 200 mg t.i.d. and the unbound fraction (0.03) of DEX in human plasma, no clin. relevant metabolic interactions with other CYP substrates are predicted.

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 23 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:398802 CAPLUS
DN 140:399305
TI Absorption, distribution, metabolism and excretion of the cholecystokinin-1 antagonist dexloxiglumide in the dog
AU Webber, C.; Stokes, C. A.; Persiani, S.; Makovec, F.; McBurney, A.; Kapil, R. P.; John, B. A.; D'Amato, M.; Chasseaud, L. F.
CS Drug Metabolism and Pharmacokinetics, Huntingdon Life Sciences, Huntingdon, UK
SO European Journal of Drug Metabolism and Pharmacokinetics (2004), 29(1), 15-23
CODEN: EJDPD2; ISSN: 0378-7966
PB Medecine et Hygiene
DT Journal
LA English
AB Single oral doses of 14C-dexloxiglumide were rapidly and extensively absorbed in dogs and also eliminated rapidly with a short half-life. Following single i.v. doses, dexloxiglumide was characterized as a drug having a high clearance (30.7 and 27.0 mL/min/kg in males and females resp.), a low volume of distribution (Vss, 0.34 and 0.27 L/kg in males and females resp.) and a moderate systemic availability (about 33%). It was extensively bound to plasma proteins (89%). Dexloxiglumide is mainly cleared by the liver. Its renal clearance was minor. In only the kidney, liver and gastrointestinal tract, were concns. of 14C generally greater than those in plasma. 14C concns. generally peaked at 0.25h and declined rapidly during 24h being present only in a few tissues (such as the kidney, liver and gastrointestinal tract) at 24h. Single i.v. or oral doses were mainly excreted in the feces (77-89%), mostly during 24h. Urine contained up to 7.5% dose. Mean recoveries during 7 days ranged between 93-97%. Biliary excretion of 14C was prominent (64% dose during 24h) in the disposition of 14C which was probably also subjected to some limited enterohepatic circulation. Unchanged dexloxiglumide was the major component in plasma. Urine and feces contained several 14C-components amongst which unchanged dexloxiglumide was the most important (eg. about 55% dose in feces). LC-MS/MS of urine and bile exts. showed that dexloxiglumide was metabolized mainly by O-demethylation and by conjugation with glucuronic acid.

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 24 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:392318 CAPLUS
DN 140:400077
TI Pharmaceutical combinations including either a 5-HT4 receptor agonist or

antagonist or a 5-HT3 receptor antagonist and a co-agent and their use in treating gastrointestinal and abdominal visceral disorders
IN Billstein, Stephan Anthony; Dumovic, Peter; Franco, Nicola; Iwicki, Mark Thomas; Pfannkuche, Hans-Jurgen; Wilusz, Edward Joseph
PA USA
SO U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 722,784, abandoned.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004092511	A1	20040513	US 2003-702688	20031106
PRAI US 1999-266333P	P	19991210		
US 2000-722784	B1	20001127		

AB The invention discloses a combination of a first agent including either a 5-HT4 receptor agonist or antagonist or a 5-HT3 receptor antagonist and a co-agent and pharmaceutical compns. and formulations containing the combination. The invention also discloses a method for treating a gastrointestinal and abdominal visceral disorder by administering the pharmaceutical compns. to a patient. The pharmaceutical compns. may also be employed as laxatives, to prepare a patient for colonoscopy and to regulate and stabilize enterochromaffin cell secretory, pain and motility mechanisms, afferent fiber activity and GI and lower abdominal smooth muscle cells. The dosage is preferably oral and administration is preferably once or twice a day. The preferred first agent is tegaserod.

L1 ANSWER 25 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:230356 CAPLUS
DN 140:332811
TI Stomach-brain communication by vagal afferents in response to luminal acid backdiffusion, gastrin, and gastric acid secretion
AU Danzer, Marion; Jocic, Milana; Samberger, Claudia; Painsipp, Evelin; Bock, Elisabeth; Pabst, Maria-Anna; Crailsheim, Karl; Schicho, Rudolf; Lippe, Irmgard T.; Holzer, Peter
CS Departments of Experimental and Clinical Pharmacology, Zoology, University of Graz, Graz, A-8010, Austria
SO American Journal of Physiology (2004), 286(3, Pt. 1), G403-G411
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB Vagal afferents play a role in gut-brain signaling of physiol. and pathol. stimuli. Here, the authors investigated how backdiffusion of luminal HCl or NH4OH and pentagastrin-stimulated acid secretion interact in the communication between rat stomach and brain stem. Rats were pretreated i.p. with vehicle or appropriate doses of cimetidine, omeprazole, pentagastrin, dexloxiglumide (CCK1 receptor antagonist), and itriglumide (CCK2 receptor antagonist) before intragastric administration of saline or backdiffusing concns. of HCl or NH4OH. Two hours later, neuronal activation in the nucleus of the solitary tract (NTS) and area postrema was visualized by c-Fos immunohistochem. Exposure of the rat gastric mucosa to HCl (0.15-0.5 M) or NH4OH (0.1-0.3 M) led to a concentration-dependent expression of c-Fos in the NTS, which was not related to gender, gastric mucosal injury, or gastropyloric motor alterations. The c-Fos response to HCl was diminished by cimetidine and omeprazole, enhanced by pentagastrin, and left unchanged by dexloxiglumide and itriglumide. Pentagastrin alone caused an omeprazole-resistant expression of c-fos, which in the NTS was attenuated by itriglumide and prevented by dexloxiglumide but in the area postrema was reduced by dexloxiglumide and abolished by itriglumide. The authors conclude that vagal afferents transmit physiol. stimuli (gastrin) and pathol. events (backdiffusion of luminal HCl or NH4OH) from the stomach to

the brain stem. These communication modalities interact because, firstly, acid secretion enhances afferent signaling of gastric acid backdiffusion and, secondly, gastrin activates NTS neurons through stimulation of CCK1 receptors on vagal afferents and of CCK2 receptors on area postrema neurons projecting to the NTS.
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 26 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:797509 CAPLUS
DN 140:292413
TI Characterization of dexloxiglumide in vitro biopharmaceutical properties and active transport
AU Tolle-Sander, Sanna; Grill, Andreas; Joshi, Hemant; Kapil, Ram; Persiani, Stefano; Polli, James E.
CS Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD, 21201, USA
SO Journal of Pharmaceutical Sciences (2003), 92(10), 1968-1980
CODEN: JPMSAE; ISSN: 0022-3549
PB Wiley-Liss, Inc.
DT Journal
LA English
AB The objective of this work was to characterize dexloxiglumide biopharmaceutical properties in vitro and relate these characteristics to its in vivo absorption performance, and to assess dexloxiglumide interaction with P-glycoprotein (P-gp) and MRP1 to anticipate its drug interaction potential. Dexloxiglumide aqueous solubility was moderate and pH dependent. Dexloxiglumide exhibited moderate Caco-2 permeability that was polarized, concentration dependent, and pH dependent. The apical-to-basolateral (AP-BL) permeability at pH 5 [14.5 (±1.8) + 10-6 cm/s] was 2-fold higher than at pH 7.5 [7.24 (±0.27) + 10-6 cm/s]. Neutral and ionized dexloxiglumide species displayed permeabilities of 30.8 (±8.4) + 10-6 cm/s and 9.03 (±1.31) + 10-6 cm/s, resp. The transport of dexloxiglumide across MDR1-MDCK (P-gp overexpressing Madine Darby canine kidney cells) monolayers was polarized, with a BL-AP/AP-BL permeability ratio of 9.35 (±0.73), which was reduced to 1.03 (±0.03) by P-gp inhibition. Rhodamine 123 efflux was reduced by dexloxiglumide from 4.06 (±0.34) to 2.84 (±0.15) across Caco-2 monolayers, and from 17.3 (±0.9) to 8.26 (±1.38) across MDR1-MDCK monolayers, further indicating dexloxiglumide interaction with P-gp. Addnl., P-gp ATPase activity increased with dexloxiglumide concentration Dexloxiglumide was effluxed from MRP1-NIH3T3 cells (NIH-3T3 cells expressing the multidrug resistance-associated protein 1). Dexloxiglumide increased MRP1-substrate fluorescein uptake 4-fold, and fluorescein increased dexloxiglumide uptake 1.8-fold. Overall, in vitro transport studies indicate dexloxiglumide to be moderately soluble and moderately permeable, which is in agreement with the incomplete oral absorption of dexloxiglumide. In vitro, dexloxiglumide was moderately modulated by P-gp and MRP1, which provides a rationale for the design of drug interaction studies.
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 27 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:776659 CAPLUS
DN 140:192141
TI Absorption, distribution, metabolism and excretion of the cholecystokinin-1 antagonist dexloxiglumide in the rat
AU Webber, C.; Stokes, C. A.; Persiani, S.; Makovec, F.; McBurney, A.; Kapil, R. P.; John, B. A.; Houchen, T. L.; D'Amato, M.; Chasseaud, L. F.
CS Drug Metabolism and Pharmacokinetics, Huntingdon Life Sciences, Huntingdon, UK
SO European Journal of Drug Metabolism and Pharmacokinetics (2003), 28(3),

201-212
CODEN: EJDPD2; ISSN: 0378-7966
PB Medecine et Hygiene
DT Journal
LA English
AB Single oral doses of 14C-dexloxiglumide were rapidly and extensively absorbed in rats, and eliminated more slowly by females than by males. The resp. half-lives were about 4.9 and 2.1h. Following single i.v. doses, dexloxiglumide was characterized as a drug having a low clearance (6.01 and about 1.96 mL/min/kg in males and females resp.), a moderate volume of distribution (Vss, 0.98 and about 1.1 L/kg in males and females resp.) and a high systemic availability. It was extensively bound to plasma proteins (97%). Dexloxiglumide is mainly cleared by the liver. Its renal clearance was minor. In only the liver and gastrointestinal tract, were concns. of 14C generally greater than those in plasma. Peak 14C concns. generally occurred at 1-2h in males and at 2-4h in females. Tissue 14C concns. then declined by severalfold during 24h although still present in most tissues at 24h but only in a few tissues (such as the liver and gastrointestinal tract) at 168h. Decline of 14C was less rapid in the tissues of females than in those of males. Single i.v. or oral doses were mainly excreted in the feces (87-92%), mostly during 24h and more slowly from females than from males. Urines contained less than 11% dose. Mean recoveries during 7 days when 14C was not detectable in the carcass except in one female rat ranged between 93-101%. Biliary excretion of 14C was prominent (84-91% dose during 24h) in the disposition of 14C which was also subjected to facile enterohepatic circulation (74% dose). Metabolite profiles in plasma and selected tissues differed. In the former, unchanged dexloxiglumide was the major component whereas in the latter, a polar component was dominant. Urine, bile and feces contained several 14C-components amongst which unchanged dexloxiglumide was the most important (eg. up to 63% dose in bile). LC-MS/MS showed that dexloxiglumide was metabolised mainly by hydroxylation in the N-(3-methoxypropyl)pentyl sidechain and by O-demethylation followed by subsequent oxidation of the resulting alc. to a carboxylic acid.
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 28 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:566592 CAPLUS
DN 139:332309
TI Pharmacokinetics and metabolism of the cholecystokinin antagonist dexloxiglumide in male human subjects
AU Webber, C.; Roth, A.; Persiani, S.; Peard, A. J.; Makovec, F.; Kapil, R. P.; John, B. A.; Holding, J. D.; D'Amato, M.; Cybulski, Z. R.; Chasseaud, L. F.; Rovati, L. C.
CS Drug Metabolism and Pharmacokinetics, Huntingdon Life Sciences, Huntingdon, PE28 4HS, UK
SO Xenobiotica (2003), 33(6), 625-641
CODEN: XENOBH; ISSN: 0049-8254
PB Taylor & Francis Ltd.
DT Journal
LA English
AB 1. Mean concns. of total 14C and of dexloxiglumide at the end of single 20-min infusion doses of 14C-dexloxiglumide (200mg) to four healthy male subjects were 18.5 μg eq.ml-1 and 19.5 μg ml-1, resp. The mean plasma clearance (0.221 h-1 kg-1) and mean volume of distribution (Vss = 0.181 kg-1) were low. 2. Single oral doses of a solid formulation of 14C-dexloxiglumide (200mg) to the same subjects appeared to be rapidly and well absorbed. Mean peak plasma concns. (Cmax) of total 14C (2.8 μg eq.ml-1) and of dexloxiglumide (2.2 μg ml-1) occurred at about 1.5 h. Systemic availabilities of the oral dose based on total 14C and dexloxiglumide were 70 and 48%, resp. Thus, a proportion of an oral dose was subjected to presystemic elimination and the absorbed dose mainly eliminated by metabolism Binding of

dexloxiglumide to plasma proteins was extensive (96.6-99.2%). 3. Total 14C was excreted mainly in the faeces. Mass balance of 14C excretion was almost complete within 7 days when a mean of > 93% of the dose had been recovered. After the i.v. dose, mean totals of 23.7 and 69.8% of the dose were excreted in urine and faeces, resp., during 7 days, and 19.5 and 73.7% of the dose, resp., after the oral dose. The data were consistent with biliary excretion and perhaps some enterohepatic circulation of conjugates of dexloxiglumide and at least one of its metabolites. 4. LC-MS/MS of urine exts. showed that dexloxiglumide was metabolized by oxidation and conjugation. The former included at least two metabolites formed by monohydroxylation in the N-(3-methoxypropyl) pentyl side chain, and O-demethylation of this side chain followed by subsequent oxidation of the resultant alc. to the dicarboxylic acid. At least one glucuronide was also present in urine. The main components in feces appeared to be dexloxiglumide and a dicarboxylic metabolite formed by O-demethylation followed by oxidation of the N-(3-methoxypropyl) side chain. Both compds. were identified as their corresponding Me esters formed because acid and methanol were used in the extraction procedure. Dexloxiglumide and the dicarboxylic acid were presumably excreted in bile as the glucuronic acid conjugates.

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 29 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:118974 CAPLUS
DN 139:17048
TI Development and validation of a bioanalytical method for the determination of the cholecystokinin type-1 (CCK1) receptor antagonist Dexloxiglumide in human plasma
AU Brodie, R.; Peard, A.; Roth, A.; Persiani, S.; Makovec, F.; D'Amato, M.
CS Department of Bioanalysis, Huntingdon Life Sciences, Huntingdon, PE28 4HS, UK
SO Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2003), 784(1), 91-100
CODEN: JCBAAI; ISSN: 1570-0232
PB Elsevier Science B.V.
DT Journal
LA English
AB A sensitive bioanal. method for the measurement of Dexloxiglumide, a new selective and potent cholecystokinin type-1 (CCK1) receptor antagonist, in plasma is reported. The method is based on reversed-phase liquid chromatog. with UV absorption detection. Samples are extracted under acidic conditions into an organic solvent, and following evaporation, reconstitution, and centrifugation stages, the supernatant is injected onto an ODS column with detection at 244 nm. The method has been validated over the concentration range 0.2-20 μg/mL, 0.2 μg/mL being the lower limit of quantification. The overall precision and accuracy (expressed as relative error) of the method was <6.1 and 2.3%, resp. Dexloxiglumide was shown to be stable in plasma when stored at -20° for at least 200 days. The method is suitable for studying the pharmacokinetics of Dexloxiglumide in man.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 30 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:580170 CAPLUS
DN 138:130403
TI Loxiglumide. Rotta Research
AU Katschinski, Martin
CS Department of Gastroenterology and Endocrinology, Philipps-University Marburg, Marburg, 35033, Germany
SO IDrugs (2002), 5(5), 469-474
CODEN: IDRUFN; ISSN: 1369-7056
PB Current Drugs Ltd.
DT Journal; General Review

LA English
AB A review. Rotta was developing loxiglumide, a competitive cholecystokinin (CCK) antagonist, for potential use in the treatment of cancer, gastrointestinal disease, eating disorders, and pancreatitis. However, by Apr. 2002 its development for indications other than acute and chronic pancreatitis had been discontinued in favor of the D-enantiomer, dexloxiglumide, which is in clin. trials for gastrointestinal disorders. Loxiglumide is awaiting approval in Japan where it is being developed for acute and chronic pancreatitis by Mitsubishi Pharma and Kaken Pharmaceuticals, resp. By Sept. 1999, Kaken had submitted a Japanese NDA for the i.v. formulation for acute pancreatitis; approval was still pending in May 2001. At this time, the oral formulation was still "pre-NDA". By Feb. 2000, loxiglumide had also been field for approval in Japan for the treatment of acute pancreatitis by Mitsubishi-Toky and was still awaiting approval in Oct. 2001. In Dec. 2001, analysts at Merrill Lynch predicted launch of loxiglumide in early 2002 for acute pancreatitis and late 2004 for chronic pancreatitis, with sales of ¥ 1 billion in 2003 rising to ¥ 6 billion in 2006.
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 31 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:580010 CAPLUS
DN 137:149660
TI Dexloxiglumide (Rotta Research Lab)
AU Varga, Gabor
CS Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, 1450, Hung.
SO Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2002), 3(4), 621-626
CODEN: COIDAZ; ISSN: 1472-4472
PB PharmaPress Ltd.
DT Journal; General Review
LA English
AB A review. Dexloxiglumide, the (R)-isomer of loxiglumide, is a selective and highly potent CCK1 receptor antagonist. It is twice as potent as the racemic compound, because the anti-CCK activity is specific to the (R)-form, whereas the (S)-isomer is almost ineffective. It has been developed by Rotta Research Lab SpA for the treatment of diseases in which CCK1 receptor activity is potentially involved, including gastrointestinal motility, food intake and pancreatic disorders [218696]. Its receptor-mediated actions have been described in multiple in vitro and in vivo pharmacol. systems. Results from both preclin. and clin. studies indicate that it is an effective inhibitor of gallbladder contraction, improves lower esophageal sphincter (LES) function, accelerates gastric emptying, accelerates colonic transit and significantly decreases symptoms in IBS and functional dyspepsia patients, and therefore has potential as an effective treatment for constipation-predominant IBS, functional dyspepsia, constipation, LES function, gastric emptying disorders and biliary colics. Forest Labs. has entered into an agreement with Rotta for the development and marketing of dexloxiglumide for the treatment of constipation-predominant IBS and phase III studies are currently ongoing in the US. In August 2000, Merrill Lynch expected that dexloxiglumide would not be launched until 2004 [379892], and in June 2001, predicted a US filing date in 2003 [413928].
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 32 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:577063 CAPLUS
DN 137:323494
TI The role of fat and cholecystokinin in functional dyspepsia
AU Fried, M.; Feinle, C.
CS Gastroenterology Division, University Hospital Zurich, Zurich, CH-8091, Switz.

SO Gut (2002), 51(Suppl. 1), i54-i57
CODEN: GUTTAK; ISSN: 0017-5749
PB BMJ Publishing Group
DT Journal
LA English
AB A subgroup of patients with functional dyspepsia are characterized by heightened visceral sensitivity to mech. distension of the stomach with a balloon. Small intestinal infusion of nutrients, particularly fat, exacerbates this hypersensitivity and also modulates sensations, such as hunger and fullness, in healthy subjects. Previous studies in healthy subjects suggest that cholecystokinin (CCK)-A and serotonergic (5-HT3) receptors mediate, at least in part, the effects of lipid on gastrointestinal sensations. Recent studies have shown that duodenal fat infusion causes a dose dependent increase in the intensity of sensations and symptoms during gastric distension. However, fat digestion, achieved by using the specific lipase inhibitor tetrahydrolipstatin (THL) is necessary to promote the effects of fat on visceral sensation, gastric relaxation, and CCK release. The digestion products of fat interact with receptors in the small intestine. Long chain triglycerides (LCT) appear to be more potent than medium chain triglycerides (MCT) in inducing symptoms of fullness, nausea, and suppression of hunger. The effects of LCT are at least partially mediated by CCK as MCTs do not cause CCK release. In patients with functional dyspepsia, gastrointestinal symptoms induced by duodenal lipid infusion and gastric distension are alleviated by the CCK-A receptor antagonist dexloxiglumide. These studies provide important insights into the mechanisms underlying gastrointestinal perception in response to fat and the role of CCK in healthy subjects and patients with functional dyspepsia.
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 33 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:537713 CAPLUS
DN 137:103303
TI New and emerging treatments for irritable bowel syndrome and functional dyspepsia
AU Talley, Nicholas J.
CS Department of Medicine, University of Sydney and Nepean Hospital, Penrith, NSW 2751, Australia
SO Expert Opinion on Emerging Drugs (2002), 7(1), 91-98
CODEN: EOEDA3
PB Ashley Publications Ltd.
DT Journal; General Review
LA English
AB A review. The symptomatic management of irritable bowel syndrome (IBS) and functional dyspepsia, which often overlap, can be frustrating and difficult. Education and reassurance remain central for management although controlled trials are lacking. Psychol. interventions may be useful in select patients but methodol. inadequacies in clin. trials limit their interpretability. For symptom exacerbations, drug treatment is reasonable but no current treatment successfully targets the full symptom complex. Bulking agents are not of proven efficacy in IBS; they may improve constipation but worsen bloating and pain. Anticholinergics are of uncertain value in IBS. A meta-anal. of trials of smooth muscle relaxants for IBS has been reported to be pos. but the quality of the trials included was poor. Antidepressants for IBS and functional dyspepsia appear to be efficacious based on the limited published evidence; both global symptoms and abdominal pain improve. Selective serotonin reuptake inhibitors (SSRIs) are of uncertain efficacy but anecdotally appear to be useful. Laxatives are not of proven efficacy in IBS. Loperamide improves diarrhea, but not abdominal pain in IBS. No drug is of proven-efficacy for bloating. Acid suppression remains the mainstay of therapy for functional dyspepsia but the majority of patients do not have an adequate response. Promising drugs include new prokinetics for constipation-predominant IBS (e.g., tegaserod, a partial 5-HT4

agonist, prucalopride, a full 5-HT4 agonist, and dexloxiglumide, a cholecystokinin 1 antagonist), agents for diarrhea-predominant IBS (e.g., 5-HT3 antagonists, α2 receptor agonists and corticotrophin receptor-1 antagonists), other visceral analgesics (e.g. tachykinin antagonists, opioid agonists) and in dyspepsia fundus relaxing agents (e.g., 5-HT1 agonists, tegaserod).

RE.CNT 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 34 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:485631 CAPLUS
DN 138:66134
TI Pharmacokinetics of dexloxiglumide after administration of single and repeat oral escalating doses in healthy young males
AU Persiani, S.; D'Amato, M.; Makovec, F.; Tavares, I. A.; Bishai, P. M.; Rovati, L. C.
CS Rotta Research Laboratorium, Monza, Italy
SO International Journal of Clinical Pharmacology and Therapeutics (2002), 40(5), 198-206
CODEN: ICTHEK; ISSN: 0946-1965
PB Dustri-Verlag Dr. Karl Feistle
DT Journal
LA English
AB This work assessed the pharmacokinetics, safety and tolerability of dexloxiglumide, a new CCK1 receptor antagonist currently under development for the treatment of the constipation-predominant irritable bowel syndrome. Volunteers received orally 100, 200 and 400 mg dexloxiglumide as tablets as a single dose, followed by repeated doses 3 times daily for 7 days according to a randomized, double-blind, double-dummy complete crossover design. Plasma and urine were collected before and for ≤72 h after administration. Plasma and urinary drugs concns. were determined by validated HPLC methods with UV detection and were used for pharmacokinetic anal. by standard noncompartmental methods. In addition, the drugs's safety and tolerability were evaluated throughout by performing standard laboratory tests, by recording vital signs and ECGs and by monitoring the occurrence and severity of adverse events. After a single oral administration, dexloxiglumide was rapidly bioavailable, with mean tmax ranging 0.9-1.6 h at all doses tested. The mean peak plasma concns. (Cmax) were 1.7, 5.4, and 11.9 μg/mL, and the mean areas under the plasma concentration-time curves (AUC) were 4.4, 8.6, and 18.3 μg + h/mL at the above 3 doses, resp. Apparent plasma clearance (CL/F) was 30.8, 27.2, and 21.1 L/h at these 3 doses, resp. The apparent elimination half-life from plasma (t1/2) ranged 2.6-3.3 h. The excretion of unchanged dexloxiglumide in 0-72-h urine accounted for approx. 1% of the dose, and this was true for all 3 doses. Dexloxiglumide renal clearance (CLR) averaged 0.4, 0.4, and 0.3 L/h for the 100-, 200-, and 300-mg doses, resp. After the last dose of the repeated-dose period dexloxiglumide Cmax occurred 1.1-1.6 h after drug administration and averaged 2.4, 7.1, and 15. μg/mL for the above 3 doses, resp. The AUC values averaged 5.9, 16.0, and 50.8 μg + h/mL, resp. The area under the plasma concentration-time curve calculated at steady state within a dosage interval (AUCss) averaged 4.6, 11.3, and 28.4 μg + h/mL, whereas CL/F averaged 20.3, 16.3, and 10.3 L/h, at the 3 doses, resp. Dexloxiglumide t1/2 could not be accurately calculated due to the high intersubject variability and to sustained plasma dexloxiglumide concns. that precluded the identification of the terminal phase of the plasma concentration-time profiles. However, it appeared that dexloxiglumide t1/2 was considerably prolonged at the dose of 400 mg. CLR averaged 0.4, 0.3, and 0.3 L/h for the 3 doses, resp. After a single dose, the plasma pharmacokinetics of dexloxiglumide were dose-independent in the dose range 100-400 mg. After repeated dose the pharmacokinetics of dexloxiglumide were virtually dose-independent in the dose range 100-200 mg. A slight deviation from linear pharmacokinetics was found with a dose of 400 mg. Plasma dexloxiglumide pharmacokinetics were also time-independent in the

dose range 100-200 mg, with a deviation from expectation based on the superimposition principle with a dose of 400 mg. Urinary excretion and renal clearance were both dose- and time-independent in the dose range 100-400 mg. The safety and tolerability of dexloxiglumide administered to healthy young males was good up to the maximum investigated dose of 400 mg both after single and after repeated doses. The safety and pharmacokinetic profile of dexloxiglumide when the drug is administered as single and repeated doses in the dose range 100-400 mg provides the rationale for the choice of a treatment schedule (200 mg 3 times daily) for efficacy trials in patients with (constipation-predominant) irritable bowel syndrome.

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 35 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:50662 CAPLUS
DN 136:210367
TI Effect of three nonpeptide cholecystokinin antagonists on human isolated gallbladder
AU Maselli, M. A.; Piepoli, A. L.; Pezzolla, F.; Guerra, V.; Caruso, M. L.; Mennuni, L.; Lorusso, D.; Makovec, F.
CS Experimental Pathophysiology and Pharmacology Laboratory, Scientific Institute of Gastroenterology "S. de Bellis,", Bari, Italy
SO Digestive Diseases and Sciences (2001), 46(12), 2773-2778
CODEN: DDSCDJ; ISSN: 0163-2116
PB Kluwer Academic/Plenum Publishers
DT Journal
LA English
AB Cholecystokinin is the most important stimulant of postprandial gallbladder contraction, and a regulator of gallbladder fasting tone. The aim of this study was to evaluate the effect of dexloxiglumide on isolated human gallbladder contraction induced by cholecystokinin-octapeptide and to compare this effect to that of lorglumide and amiglumide, two glutaramic acid analogs of dexloxiglumide. The neg. logarithms of the antagonist dissociation constant (pKB) values were 7.00 0.14, 6.95 0.11, and 6.71 0.10 for lorglumide, dexloxiglumide, and amiglumide, resp. Dexloxiglumide produced a concentration-dependent rightward shift of the cholecystokinin-octapeptide curve, without affecting its maximal response. A similar effect was obtained both with lorglumide and amiglumide. Moreover, the slopes for the three antagonists did not differ significantly from unity. These data show that the three mols. have a potent antagonistic effect, of a competitive nature, on gallbladder cholecystokinin type 1 receptors. It may be concluded that dexloxiglumide, lorglumide, and amiglumide exhibit a promising therapeutic profile for biliary colic and other gastrointestinal disorders in which CCK1 receptors play important physiol. roles.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 36 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:234079 CAPLUS
DN 135:193775
TI Role of duodenal lipid and cholecystokinin A receptors in the pathophysiology of functional dyspepsia
AU Feinle, C.; Meier, O.; Otto, B.; D'Amato, M.; Fried, M.
CS Gastroenterology Division, University Hospital Zurich, Zurich, 8091, Switz.
SO Gut (2001), 48(3), 347-355
CODEN: GUTTAK; ISSN: 0017-5749
PB BMJ Publishing Group
DT Journal
LA English
AB The authors aimed to evaluate the role of fat and cholecystokinin (CCK) in

the pathophysiol. of functional dyspepsia (FD) by investigating symptoms and plasma CCK levels following increasing doses of duodenal lipid during gastric distension, and the effect of CCK-A receptor blockade. In study A, 6 FD patients were studied on 3 occasions during duodenal infusion of saline or lipid (1.1 (L-1) or 2 kcal/min (L-2)) and proximal gastric distensions. 6 Healthy subjects were also studied as controls during L-2 only. In study B, the effect of the CCK-A antagonist dexloxiglumide (5 mg/kg/h) on L-2 induced symptoms was studied in 12 FD patients. Changes in gastric volume at minimal distending pressure and plasma CCK (study A) were assessed, gastric distensions were performed using a barostat, and dyspeptic symptoms were monitored. Lipid increased gastric volume compared with saline (ΔV (ml): saline 15 (20), L-1 122 (42), L-2 114 (28)) in patients and even more so in controls (221 (37); $p<0.05$). During distensions, symptoms were greater during L-2 than during saline or L-1, and greater in patients than in controls, while gastric compliance was smaller in patients than in controls ($p<0.05$). Lipid increased plasma CCK levels in patients and controls ($p>0.05$). Dexloxiglumide abolished the increase in gastric volume (ΔV (ml): dexloxiglumide 17 (9), placebo 186 (49)) and dyspeptic symptoms (sum of scores: dexloxiglumide 24 (7), placebo 44 (19)) during duodenal lipid infusion. Dexloxiglumide also reduced gastric compliance (ml/mm Hg: dexloxiglumide 51 (7), placebo 72 (11)) and symptoms (sum of scores: dexloxiglumide 101 (17), placebo 154 (21)) during gastric distension. CCK-A receptors are involved in the generation of dyspeptic symptoms by duodenal lipid during gastric distension.

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 37 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1999:656782 CAPLUS
DN 132:145945
TI Dexloxiglumide: CCK1 (CCKA) receptor antagonist treatment of irritable bowel syndrome
AU Revel, Laura; Makovec, Francesco; Castaner, J.
CS Prous Science, Barcelona, 08080, Spain
SO Drugs of the Future (1999), 24(7), 725-728
CODEN: DRFUD4; ISSN: 0377-8282
PB Prous Science
DT Journal; General Review
LA English
AB A review with 35 refs. of the synthesis and pharmacol. of dexloxiglumide, as well as its clin. studies in the treatment of irritable bowel syndrome and functional dyspepsia.
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 38 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1998:370098 CAPLUS
DN 129:90694
TI Different actions of CCK on pancreatic and gastric growth in the rat: effect of CCKA receptor blockade
AU Varga, Gabor; Kisfalvi, Krisztina; Pelosini, Iva; D'amato, Massimo; Scarpignato, Carmelo
CS Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hung.
SO British Journal of Pharmacology (1998), 124(3), 435-440
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton Press
DT Journal
LA English
AB It is now well established that cholecystokinin (CCK) has a major physiol. role in the regulation of pancreatic secretion and gastro-intestinal (GI) motility. Both these actions are mediated by stimulation of CCKA-receptors located on pancreatic acini and GI smooth muscle cells.

While chronic administration of CCK-like peptides invariably causes pancreatic hypertrophy and hyperplasia, their action on gastric growth remains controversial. In the present investigation the action of exogenous and endogenous CCK on both pancreatic and gastric growth was studied in the same animal. In addition, the ability of dexloxiglumide, a new potent and selective CCKA-receptor antagonist, to counteract CCK-mediated effects was evaluated. The amphibian peptide caerulein (1 μg kg-1 i.p. three times daily) was used as a CCK agonist, while camostate (200 mg kg-1 intragastrically once daily), a synthetic protease inhibitor, was used to release endogenous CCK. They were administered to rats for seven days with or without dexloxiglumide (25 mg kg-1 s.c. 15 min before the stimulus). On the eighth day, animals were killed, the pancreas and stomach excised, weighed, homogenized and their protein and DNA content measured. Both exogenous and endogenous CCK increased the weight of the pancreas as well as the total pancreatic protein and DNA content. Dexloxiglumide, which alone did not affect pancreatic size and composition, was able to counteract both caerulein- and camostate-induced pancreatic changes. Neither stimuli affected gastric growth in respect of weight and composition of the oxyntic gland area and the antrum. These results show different effects of CCK on pancreatic and gastric growth. The CCK-induced pancreatic hypertrophy and hyperplasia are blocked by the potent and specific CCKA-receptor antagonist, dexloxiglumide. This compound therefore represents a useful tool to investigate CCK-receptor interactions in peripheral organs.

RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 39 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1997:806296 CAPLUS
DN 128:113236
TI Effect of a new CCK-A receptor antagonist, dexloxiglumide, on the exocrine pancreas in the rat
AU Varga, G.; Kisfalvi, K.; D'Amato, M.; Scarpignato, C.
CS Hungarian Academy Sciences, Institute Experimental Medicine, Budapest, 1450, Hung.
SO Journal of Physiology (Paris) (1997), 91(3-5), 257-264
CODEN: JHYSEM; ISSN: 0928-4257
PB Editions Scientifiques et Medicales Elsevier
DT Journal
LA English
AB The effect of dexloxiglumide, a new potent cholecystokinin (CCK) antagonist, on pancreatic enzyme secretion and growth was studied in the rat. Pancreatic exocrine secretion was studied both in vitro (isolated and perfused pancreatic segments) and in vivo (anesthetized animals with cannulation of the common bile duct) whereas the trophic effect was investigated after short-term (7 days) administration of the CCK-agonist, caerulein, or camostate (a potent trypsin inhibitor), with or without dexloxiglumide. CCK-8 stimulated amylase release from in vitro pancreatic segments in a concentration-dependent manner. Dexloxiglumide displaced the concentration response curves to CCK-8 to the right without affecting the maximum response, suggesting a competitive antagonism. The Schild plot anal. of data gave a straight line with a slope (0.90±0.36) not significantly different from unity. The calculated pA2 for dexloxiglumide was 6.41±0.38. In vivo expts. confirmed results from in vitro studies since i.v. dexloxiglumide reduced pancreatic exocrine secretion induced by submaximal CCK-8 stimulation (0.5 nmol/kg/h) in a dose-dependent manner, the ID50 being 0.64 mg/kg. Both exogenous and endogenous (released by camostate) CCK increased the weight of the pancreas, the total pancreatic protein and DNA, trypsin and amylase content. Dexloxiglumide (25 mg/kg), administered together with caerulein (1 μg/kg), reduced the peptide-induced increase in pancreatic weight, protein and enzyme content. Similarly, when dexloxiglumide was given together with camostate (200 mg/kg), all the observed changes were reduced by concomitant administration of the antagonist. These results

demonstrate the ability of dexloxiglumide to antagonize the effects of CCK on pancreatic secretion and growth, suggesting that this compound is a potent and selective antagonist of CCK-A-receptors in the pancreas.

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 40 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1996:398396 CAPLUS
DN 125:75969
TI Effect of dexloxiglumide and spiroglumide, two new CCK-receptor antagonists, on gastric emptying and secretion in the rat: Evaluation of their receptor selectivity in vivo
AU Scarpignato, C.; Kisfalvi, I.; D'Amato, M.; Varga, G.
CS School Medicine and Dentistry, University Parma, Italy
SO Alimentary Pharmacology and Therapeutics (1996), 10(3), 411-419
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell
DT Journal
LA English
AB The availability of such compds. has stimulated a broad array of investigations into the physiol. actions of this hormone and to examine its putative role in certain diseases. The effect of two recently developed CCK-receptor antagonists, namely dexloxiglumide and spiroglumide, on gastric emptying and secretion as well as their selectivity towards CCKA - and CCKB-receptors in vivo was studied in the rat. Gastric emptying was quantified by using a liquid noncaloric meal labeled with phenol red. Acid secretion was measured by titration in conscious rats. The putative CCKA-antagonist, dexloxiglumide, administered by i.v. route, was able to inhibit CCK-8-induced delay of gastric emptying in a dose-dependent fashion, with an ID50 (95% CL) of 1.14 (0.84-1.53) mg/kg. Similarly, the putative CCKB-gastrin-antagonist, spiroglumide, proved to be capable of inhibiting dose-dependently pentagastrin-induced acid hypersecretion, its ID50 being 20.1 (8.67-46.4) mg/kg. Dexloxiglumide, at doses able to almost completely block CCKA mediated effects (i.e. delay of gastric emptying), was ineffective against pentagastrin-induced acid hypersecretion. Similarly, spiroglumide, at doses which inhibit by 55% CCKB-gastrin mediated effects (i.e. acid secretion) was inactive when tested against CCK-8 induced delay of gastric emptying. These results demonstrate in vivo that dexloxiglumide is a selective antagonist for CCKA-receptors whereas spiroglumide is selective for CCKB-gastrin-receptors. These compds. are therefore useful tools for discriminating between different subclasses of CCK-receptors in vivo and might have a therapeutic potential in motility or acid-related disorders.

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---Logging off of STN---

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	116.15	116.36

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION